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However, the fact that the fibers can form in a cell-free ground substance shows that no part of the cell cytoplasm is necessary for their differentiation from the ground substance.

5. Any satisfactory theory of connective tissue formation must take into account the well-established fact that the great mass of the connective tissues, both ground substance and fibers, is formed when not in contact with cells. The adherents of the intracellular theory of connective tissue formation, holding that both ground substance and fibers are living material, although of a different grade from that in cells, maintain that the embryonic connective tissue after it has been formed by an intracellular action has the power to grow through the assimilation of food material, and the ability to differentiate new fibers.[4]

6. The results of the present researches may be summarized as follows:

(*a*) The origin of connective tissue lies in an intercellular secretion of the embryonic cells. This secretion constitutes the ground substance of the connective tissues and it increases in amount during development not by an assimilation of food materials and consequent growth but by the continued and additional secretions given off by the embryonic cells.

(*b*) This ground substance secreted by the cells is of such a nature that, under the influence of various chemical and mechanical factors, it forms the connective tissue fibers by means of a consolidation of the minute elements of which it is composed in apparently the same way that a transformation of the plasma clot occurs.

[1] Baitsell, G. A., (*a*) *J. Exper. Med.*, **21**, 1915 (455); (*b*) *Ibid.*, **23**, 1916 (739); (*c*) *Amer. J. Physiol.*, **44**, 1917 (109).

[2] The presence of a primitive ground substance has been demonstrated by various investigators. E.g., see Merkel, F., *Anat. Hefte*, **38**, 1908 (321); and Szily, A., *Ibid.*, **37**, 1907 (649). Both of these articles contain a full review of the literature.

[3] Harrison, R. G., *J. Exper. Zoöl.*, **17**, 1914 (521).

[4] E.g., see Heidenhain, M., *Plasma und Zelle*, pp. 33, 38, etc.

CALCIUM AND MAGNESIUM METABOLISM IN CERTAIN DISEASES

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Communicated by L. B. Mendel. Read before the Academy, November 10, 1919

We wish to present some observations upon calcium and magnesium metabolism in leprosy and in multiple exostosis.

Clinically, leprosy is characterized by a *loss* from the body of bone salts; in multiple exostosis bone salts are *added* to the organism for the calcification of the new growths. It is thus apparent that in these two abnormal conditions the processes involved in calcium and magnesium metabolism must stand in sharp contrast. The literature contains little data relative to mineral metabolism in either of these diseases.

In the present investigation the general plan followed was to place the subjects of experimentation upon a known diet low in calcium and magnesium for a definite period. Calcium or magnesium was then added for a second period. Calcium intake was increased by the administration of milk. Magnesium was given in the form of the citrate. By the procedure outlined it is apparent that the organism was given a distinct task to perform. The manner in which this task was accomplished by the diseased organism was judged by comparison with normal subjects maintained under similar experimental conditions.

The experiments were made upon six subjects divided as follows:

(*a*) 2 normal subjects. (*b*) 2 leprous subjects. (*c*) 2 exostosis subjects.

In the study of leprosy one subject represented a well-advanced case; in the other the disease was in an incipient stage.

With exostosis one subject had advanced to the stage where the abnormal processes had become stabilized; the other case represented the active, less advanced stage of the disease.

Results.—When compared to normal individuals under the same experimental conditions leprous patients retain calcium in relatively large quantities whether the individual is maintained upon a calcium-poor or a calcium-rich diet; and the greater the intake of calcium the greater is the relative retention. In the more advanced stage of the disease the degree of retention is greater than in the early phase.

This retention cannot be explained by differences in calcium intake or by variation in the power of absorption. It is apparently an evidence of a metabolic demand for calcium induced by the disease. Clinically, it may be inferred that there is a need for calcium; experimentally, the organism gives evidence of this need by retention of calcium administered.

The study of magnesium exchange in normal and leprous subjects demonstrates that in the advanced stage of leprosy there is a tendency for a retention of magnesium. The degree of retention is much less marked than in the case of calcium.

With the exception of the retention of calcium and magnesium the leprous organism responds to changes in intake of calcium and magnesium in the same manner as that exhibited by the normal subject.

It is, perhaps, self-evident that the loss of bone salts in leprosy is but a manifestation of the disease processes. Nevertheless it is quite conceivable in dietary conditions where calcium is not particularly abundant that the lack of this element may play a material rôle in the rapidity of the progress of the disease. Conversely, the suggestion is pertinent that the progress of the disease may be greatly retarded or perhaps even alleviated if an abundance of calcium is present in the diet.

The suggestion that plenty of calcium and magnesium be supplied in the food in leprosy as a therapeutic measure is at least worthy of trial.

Multiple Exostosis.—From a consideration of the study of multiple exostosis it may be concluded that in the stabilized stage of this disease calcium exchange differs little from that of a normal individual whether the abnormal subject is maintained upon a calcium-poor or a calcium-rich diet.

In the progressive stage of the disease calcium metabolism is markedly different from the normal in that calcium is lost from the body in relatively large amounts when the subject is maintained upon a calcium-poor diet. This excessive elimination of calcium is excreted by both the urine and feces in a normal ratio. When placed on a calcium-rich diet calcium is retained in the body to an extent not widely deviating from that obtaining in normal subjects. A resumption to a calcium-poor diet again induces excessive calcium elimination.

In the stabilized stage of multiple exostosis magnesium excretion is two or three times as great as the intake whether the subject is maintained upon a diet poor or rich in magnesium.

In the progressive stage of the disease the general type of magnesium excretion resembles that of the stabilized stage but the *degree* of elimination is not so marked.

Magnesium added to the diet in the stabilized stage results in the prompt excretion of the same. The same test applied to the progressive stage gives evidence of the retention of some magnesium. The degree of retention, however, is much less than that shown by normal individuals.

Absorption of both calcium and magnesium in multiple exostosis is not inferior to that of normal subjects.

The facts enumerated suggest that in the early stages of this proliferative type of bone disease under discussion a check may perhaps be given to the progress of the disease by proper dietary procedure—restriction of calcium and magnesium intake.

Summary.—Clinically, in leprosy there is evidence of loss of bone salts; experimentally, the leprous organism gives evidence of a marked tendency to retain or conserve bone salts, more especially calcium.

Clinically, in multiple exostosis it may be inferred that bone salts are added to the body; experimentally, in the progressive stage of the disease the organism attempts to rid itself of bone salts, particularly calcium. In the stabilized stage the organism throws out excessive quantities of magnesium.

These facts suggest possible beneficial results in treatment by the institution of proper dietary procedures.